THE OFFICE OF PESTICIDE PROGRAMS' GUIDANCE DOCUMENT

ON

METHODOLOGY for DETERMINING the DATA NEEDED and the TYPES of ASSESSMENTS NECESSARY to MAKE FFDCA SECTION 408 SAFETY DETERMINATIONS for LOWER TOXICITY PESTICIDE CHEMICALS

OFFICE OF PESTICIDE PROGRAMS
U.S. ENVIRONMENTAL PROTECTION AGENCY

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I. INTRODUCTION

The paper describes the newly-developed methodology that is now being used on a chemical-by-chemical basis to evaluate low toxicity chemical substances for use in pesticide products. Section 408 of the Federal Food, Drug, and Cosmetic Act (FFDCA) requires EPA to determine that there is a reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue before granting a tolerance or exemption from the requirement of a tolerance for that pesticide chemical. Both inert and active ingredients of pesticide products, and their metabolites and degradates are considered "pesticide chemicals"

The Office of Pesticide Programs (OPP) is the Office within the Environmental Protection Agency (EPA or the Agency) responsible for evaluating pesticide products under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and FFDCA. OPP's responsibilities (all of which could be affected by the use of this new methodology) include:

- Registration of new active ingredients
- Reregistration of older active ingredients
- Reassessment of both tolerances and tolerance exemptions
- Approval of new inert ingredients
- List reclassification of inert ingredients.

Development of this methodology began as a result of OPP's need to (1) develop a new methodology for assessing inert ingredients (sometimes referred to as other ingredients) to comply with the requirements of the Food Quality Protection Act (FQPA) of 1996 which amended both FFDCA and FIFRA and (2) improve the efficiency and effectiveness of the inert review process. The methodology described herein is an evolution, advancement, and refinement of the approach described in the 1987 and 1989 inert ingredient policy statements (April 22, 1987; 52 FR 13305 and November 22, 1989; 54 FR 48314). It should be noted that the term inert ingredients or inerts is used throughout this paper; however, as will be explained this methodology is appropriate for most low toxicity chemicals whether used as inert or active ingredients.

EPA believes that FFDCA section 408 safety determinations can be made for many low or low/moderate toxicity inert ingredients based on significantly fewer data than would be needed for inert ingredients of higher potential toxicity. This paper explains the process EPA is now using for making chemical-by-chemical decisions for these lower toxicity chemicals substances concerning how much and what kinds of data are necessary to support a petition for, or reassessment of, an exemption from the requirement of a tolerance.

In many instances, a chemical can be used as an inert ingredient in some pesticide products and as an active ingredient in other pesticide products. Since FFDCA section 408 makes no distinction between active and inert ingredients of a pesticide product, EPA may use this tiered data screening methodology when evaluating any pesticide chemical of apparent low or low/moderate toxicity, regardless of whether it might be characterized as an active or inert ingredient.

At this time, EPA has completed review of two tolerance exemption petitions and over 200 tolerance reassessments for low or low/moderate toxicity chemicals using essentially the process described in this paper. More reviews are underway. Based on these experiences, OPP intends to continue its chemical-by-chemical reviews of pesticide chemicals according to the process described herein for the foreseeable future. However, EPA remains interested in further improvements in the efficiency and reliability of its process, and therefore welcomes comments from interested persons.

This paper is intended to provide guidance to EPA personnel and decision-makers, and to pesticide registrants. The policies and process described herein are not binding on either EPA or pesticide registrants, and EPA may modify or disregard the process described herein where circumstances warrant and without prior notice. Likewise, pesticide registrants may assert that this process is not appropriate generally or not applicable to a specific pesticide chemical or situation.

II. BRIEF OVERVIEW of NEWLY DEVELOPED METHODOLOGY

The methodology currently being used by OPP for evaluating low or low/moderate toxicity chemical substances is a screening process that incorporates elements of a tiered data approach. In establishing this process, the Office of Pesticide Programs sought a framework that would allow decisions to be based on sound science and achieve the risk characterization principles of transparency, clarity, consistency, and reasonableness. There is also a need for these decisions to be made in an efficient and cost-effective manner.

After evaluating several alternatives, OPP believes that a screening methodology is the most appropriate way to handle the variety of hazard and exposure issues posed by inert ingredients. This screening methodology will allow OPP to make decisions in a streamlined manner for low or low/moderate toxicity chemical substances. By being able to quickly review and approve the use of these chemical substances, more low or low/moderate toxicity chemical substances will be available for use in pesticide products. OPP will also be able to focus its resources on those chemical substances of potentially higher toxicity requiring in-depth evaluation.

OPP has incorporated elements of a tiered data approach into this methodology. This tiered data approach differs from the tiered approach of 40 CFR 158.101, where a basic set of data is required for every chemical substance and additional data may be required based on the results of the review of the initially required data. Instead, OPP would use existing information on the hazard potential (both human health and ecological) of a chemical substance as the basis for deciding if additional data are needed to support the use of the chemical. The hazard potential - the toxicity - is the driving force in determining tier placement. Chemical substances that are of low or low/moderate toxicity may be appropriately placed in a lower tier, with fewer data needed to make the safety finding. Chemicals of higher toxicity that can not be appropriately addressed in the lower tiers would be evaluated in a manner substantially similar to that of an active ingredient.

In its evaluations, OPP also considered that some chemicals may be used as an inert ingredient in some formulations and as an active ingredient in other formulations. EPA believes this methodology may also be appropriate for evaluating some low toxicity chemicals regardless of whether they are categorized as active or inert ingredients.

The methodology described in this paper, as currently in use by OPP, has three tiers, with the first tier being subdivided into Tiers1a and 1b. The process begins with a preliminary Tier determination that is based on widely available information on chemical families and categories. Later as the Agency begins to review chemical-specific or surrogate information in the open literature, the preliminary Tier determination may be revised.

Tier 1 chemicals would be those of low or low/moderate toxicity for which there is readily available scientifically-valid information/data to make a confirmatory judgement

concerning these chemical substances' low or low/moderate toxicity. It is anticipated that the rationale and justification used to make this confirmatory judgement concerning the low or low/moderate toxicity for these chemicals would consist of commonly or readily available knowledge on the lack of toxicity. This could include information such as a review of existing data, or a SAR (structure-activity-relationship) assessment. Tier 1a risk assessments will be qualitative. Tier 1b risk assessments will usually be qualitative, although for some lower toxicity chemical substances a quantitative risk assessment may be performed.

Tier 2 chemicals would be those for which OPP does not have and cannot locate sufficient information to assess the chemical substance's toxicity. Given the lack of readily available information to classify it as a Tier 1, the chemical substance would be placed in Tier 2, and OPP would likely require the submission of a limited data set to characterize the hazard of the chemical substance. This data set would have similarities to the internationally recognized Organization for Economic Cooperation and Development (OECD) Screening Information Data Set (SIDS). The data submitted could be either existing studies that were not readily available to OPP or newly performed studies. Once the submitted data have been reviewed and evaluated, the Tier 2 determination could be revised to either Tier 1 or Tier 3. For most Tier 2 chemical substances, the quantitative risk assessment would integrate the results of the submitted studies, a SAR assessment, and any relevant existing data (if available). However, it is also possible that some Tier 2 chemicals could have qualitative assessments based upon the review and evaluation of the submitted data.

Chemical substances which appear to have appreciable toxicity would be assigned to Tier 3. The methodology discussed in this paper is not appropriate for making FFDCA Section 408 safety determinations for higher toxicity chemical substances. OPP anticipates that it would need to review a complete (food-use) 40 CFR Part 158 database to make these safety determinations.

It should be emphasized that a Tier determination is merely a tool used by OPP to assist in making its decisions on how to evaluate the risk of a chemical substance. In and of itself, the Tier Determination has little regulatory meaning. In fact, this methodology could be performed without formal tiers; however, OPP has found it to be a useful tool in its internal discussions.

III. BACKGROUND

Definition of Inert Ingredient

"Inert ingredients" are all ingredients contained in a pesticide product that are not "active ingredients" as defined in 40 CFR 153.125. These substances have a very wide range of physical/chemical characteristics and potential toxicological effects ranging from practically non-toxic to effects of high toxicological concern, such as carcinogenicity. One of the most significant challenges EPA faced in developing a methodology for a comprehensive inert ingredient assessment program was determining the most appropriate procedure for evaluating such a diverse group of substances.

Statutory and Regulatory Framework of Pesticide Regulation

Pesticide products are regulated under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), and the Federal Food, Drug, and Cosmetic Act (FFDCA). Both statutes were amended by the Food Quality Protection Act (FQPA) of August 3, 1996.

FIFRA authorizes EPA to register a pesticide if among other things, it will perform its intended function without unreasonable adverse effects on the environment and its composition and labeling meet requirements under FIFRA section 3(c)(5) or 3(c)(7). FIFRA prohibits the sale or distribution of any unregistered pesticides in the United States unless the Agency authorizes an emergency exemption from FIFRA requirements under section 18 of FIFRA, or issues a regulation exempting a pesticide from FIFRA requirements under section 25(b) of FIFRA. FIFRA also authorizes States, subject to EPA review, to grant special local needs registration under FIFRA section 24(c). FIFRA section 4 also requires EPA to reevaluate all pesticides first registered before November 1, 1984, through a program called reregistration.

FFDCA prohibits the introduction or delivery for introduction into interstate commerce of any food that is "adulterated" (FFDCA section 301(a)). Food is deemed adulterated if, among other reasons, "it bears or contains a pesticide chemical residue that is unsafe within the meaning of section 408(a)" (FFDCA section 402(a)(2)(B)). Under FFDCA section 408(a)(1), "any pesticide residue in or on a food shall be deemed unsafe for the purposes of section 402(a)(2)(B) unless a tolerance ....is in effect...." and residues in/on the food are within the tolerance.

FQPA clarified EPA's authority to establish a tolerance (or tolerance exemption) for residues of a pesticide active ingredient, any inert ingredient and any metabolites and degradates of active or inert pesticide ingredients that are in or on a food. FQPA redefined "pesticide chemical" in FFDCA section 201(q)(1) to mean: "any substance that is a pesticide within the meaning of FIFRA, including all active and inert ingredients of such pesticide". FQPA also added a definition of "pesticide chemical residue" in FFDCA section 201(q)(2). This term means any residue of a pesticide chemical or any other substance that results primarily from the metabolism or degradation of a pesticide chemical. This definition makes explicit the long-

standing EPA interpretation that tolerances established under section 408 of the FFDCA cover chemical compounds formed through the breakdown or metabolism of pesticidally active and inert ingredients of a pesticide formulation.

FQPA significantly changed the basis for making a safety finding when establishing a tolerance (or tolerance exemption). Under FFDCA section 408(b)(2)(A) and (c)(2)(A), the Agency must find that: "There is reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information."

In addition to assessing exposure to pesticide residues in food and water, EPA must assess exposures to pesticide residues from non-occupational uses, such as, in and around the home, garden, recreational areas, and school. Additionally, the Agency is required to assess the risk of a pesticide chemical exposure to infants and children using an additional 10-fold margin of safety to take into account potential pre-and post-natal exposures and completeness of the data with respect to exposure and toxicity for infants and children, unless EPA determines, based on reliable data, that a different margin of safety will be safe for infants and children. It is important to note that the new safety standard applies to all components of the pesticide residue on food – the active ingredient and its metabolites or degradates and all inert ingredients and their metabolites and degradates.

FFDCA also requires the Agency to review over a 10-year period which ends August 2006 all "tolerances and exemptions for pesticide chemical residues in effect on the day before the date of the enactment of the Food Quality Protection Act of 1996." In making its reassessment determination, the Agency applies a "reasonable certainty of no harm" standard.

While FIFRA governs the sale, distribution and use of a pesticide through a registration process and enforcement of the requirements on the pesticide label, FFDCA provides a direct means of policing pesticide residue levels in food through a tolerance or an exemption from tolerance for the pesticide residues. Under 40 CFR 152.112(g) and 152.113(a), EPA will not register the use of a pesticide if all needed tolerances or tolerance exemptions have not been established for each of the active and inert ingredients in the formulation.

Authority to Regulate Inert Ingredients under FIFRA and FFDCA

EPA's authority and obligation to regulate inert ingredients is clear. FFDCA section 408(q)(1) expressly includes "all active and inert ingredients" within the definition of "pesticide chemical". FIFRA section 3(c)(5) requires EPA to determine, for each individual pesticide product, whether its composition is such as to warrant the proposed claims made for it, whether it will perform its intended function without unreasonable adverse effects on the environment, and whether, when used in accordance with widespread and commonly recognized practice, it will not generally cause unreasonable adverse effects on the environment. Making such findings in regard to each individual pesticide product necessarily requires that EPA take into account the

characteristics of the inert ingredients of the pesticide.

FIFRA specifically requires the submission of various information on the inert ingredients in a pesticide formulation. FIFRA section 2(n) requires that the total percentage of all inert ingredients be listed as part of the ingredient statement on the label, and FIFRA section (3)(c)(1)(D) requires the submission of "the complete formula of the pesticide" as a condition of registration. Additionally data-call-in notices for inert ingredients are issued under FIFRA section (3)(c)(2)(B). Although regulations established in 1984 require the submission of a battery of acute toxicity tests on the pesticide formulation (which would include both the active and inert ingredients), there were no specific inert ingredient data requirements. 40 CFR 158.155(b) require the identification and characterization of the inert ingredients in a pesticide formulation. Moreover, the general requirements of the FFDCA apply equally to active and inert ingredients.

Summary of the Pesticide Program Risk Assessment and Risk Management Process

In evaluating possible impacts of pesticide exposures on human health and the environment, the Agency uses a process known as risk assessment. The National Academy of Sciences and EPA risk assessment guidelines define risk assessment as the process for analyzing scientific data to describe the form, dimension, and characteristics of risk. That is, a risk assessment answers the question: What is the likelihood of harm to humans or the environment? Risk assessments are performed in a four-step process:

- Hazard Identification/Assessment: determining whether a particular chemical is or is not linked to a particular effect
- Dose-Response Assessment: determining the relationship between the magnitude of the exposure and the probability of the particular effect occurring at a particular exposure
- Exposure Assessment: determining the nature and extent of the exposure
- Risk Characterization: a description of the nature (qualitative) and the magnitude (quantitative) of risk, including a discussion of the strengths and weaknesses of the assessment

Once the risk assessment is complete, the conclusions of the risk assessment are used to make an informed risk management determination. In managing the risk, the OPP risk manager considers the statutory requirements and the feasibility of the risk mitigation/risk reduction measures.

IV. HISTORY of the INERT REGULATORY PROGRAM

Pesticide products have a wide variety of purposes and uses. They are used at a wide variety of sites: farms and feed lots, homes and schools. Some pesticide products can be used to fumigate soil, others to kill weeds. Some are used to prevent food spoilage or insect infestation after harvest. Some products are intended to be used in small, localized spots, while others are meant to be broadcast over a large area. Some are used to kill germs on food-contact surfaces in homes, restaurants and processing facilities.

Most active ingredients cannot be used in their pure form. Generally, it is necessary to add other substances to a pesticide formulation to ensure that the active ingredient will be delivered to the target site at a consistent concentration in a controlled manner. These substances that are added to the active ingredient are referred to as inert ingredients. Examples of inert ingredients uses include:

- stickers (to increase the time that the active ingredient remains on the plant part or other solid surface),
- solvents,
- surfactants (to modify the surface characteristics, such as reducing the surface tension of water often described as wetting agents, detergents, penetrants, and emulsifiers),
- carriers such as clay and diatomaceous earth on which the active ingredient is coated,
- thickeners such as carrageenan and modified cellulose,
- propellants in aerosol dispensers; and
- encapsulating agents which can fix the active ingredient in a matrix and, thus, control its rate of release.

Although the term "inert" may connote physical, chemical or biological inactivity, use of the word "inert" to describe a component in a pesticide product means only that the substance is not intended to exert a pesticidal effect (i.e., to prevent destroy, repel or mitigate any pest or to function as a plant regulator, desiccant, or defoliant) in that product. The "inert" ingredient may have biological activity of its own, it may be toxic to humans, and it may be chemically active. However, while inert ingredients may be important in delivering the pesticide product in a controlled manner, they are not the ingredient in the formulation that is intended to prevent, destroy, repel, or mitigate the target pest.

Prior to the creation of EPA, the Food and Drug Administration (FDA) had the responsibility for establishing pesticide residue tolerances under section 408 of FFDCA. The Department of Agriculture (USDA) registered pesticides under FIFRA. USDA determined in 1961 that all ingredients in a pesticide (then referred to as an "economic poison") are "pesticide chemicals"under FFDCA and therefore residues of inert ingredients of pesticide formulations on raw agricultural commodities would be subject to section 408 of FFDCA. On April 11, 1962, FDA promulgated tolerance exemptions for substances known to be used in pesticide formulations applied to growing crops or raw agricultural commodities. Later, in 1969, a process

was established whereby persons wishing to use additional inert ingredients in food-use pesticides could submit a petition to FDA requesting approval of the use. To support the requested use, petitioners were required to submit two subchronic toxicity studies, and, for postharvest use, two chronic toxicity studies. Petitioners could ask FDA to waive some or all of these data requirements if they could demonstrate that the inert ingredient was useful in the formulation and had been previously determined to be generally recognized as safe (GRAS) for that purpose.

Many of the inert ingredients approved for food-use during the 1970s and early 1980s were approved using a data review process that was less rigorous than that used today, but was consistent with the standards of the time. In those cases where data were provided, the substances being considered for use as inert ingredients were often FDA-approved food additives for which toxicological data had already been developed.

In response to concerns that the then existing process for reviewing inert ingredients did not adequately account for potential effects on human health or on the environment, OPP reevaluated its procedures for approving inert ingredients in pesticide products. On April 22, 1987, OPP published in the Federal Register (52 FR 13305) a policy statement on inert ingredients that established four categories of toxicological concern for the inert ingredients in use at the time:

- List 1 inert ingredients were "inerts of toxicological concern." List 1 inert ingredients were classified on the basis of peer reviewed studies which demonstrated carcinogenicity, adverse reproductive effects, neurotoxicity or other chronic effects, developmental toxicity (birth defects), ecological effects and the potential for bioaccumulation.
- List 2 inert ingredients were "potentially toxic inerts/high priority for testing." Many of these inert ingredients are structurally similar to chemicals known to be toxic; some have data suggesting a concern.
- List 3 inert ingredients were "unknown toxicity." An inert ingredient was placed on List 3 if there was no basis for listing it on any of the other three lists.
- List 4 inert ingredients were "inerts of minimal concern."

On November 22, 1989, (54 FR 48314) List 4 was further subdivided into List 4A and List 4B:

- List 4A inert ingredients are minimal risk inert ingredients.
- List 4B inert ingredients are "inerts for which EPA has sufficient information to reasonably conclude that the current use pattern in pesticide products will not adversely affect public health or the environment."

The 1987 policy also specified a minimum or base set of data that would be needed to assess all new inert ingredients. These data were a subset of the data requirements for pesticide active ingredients and included:

- general information (use patterns, types of formulated products, and purpose of the inert ingredient in the formulation),
- eight product chemistry studies,
- toxicity studies
    - two 90-day (subchronic) (rat and non-rodent) feeding studies (food uses)
    - dermal subchronic (non-food uses)
    - rat developmental toxicity study
    - mutagenicity studies
- for outdoor uses only, four ecotoxicity studies
    - acute fish toxicity
    - acute invertebrate toxicity
    - acute bird toxicity
    - 8-day bird toxicity
- for outdoor uses only, five environmental fate studies
    - hydrolysis
    - aerobic soil metabolism
    - photodegradation in water
    - photodegradation in soil
    - soil adsorption/desorption (Koc or Kd)

If, during the Agency's review and evaluation, concerns were identified, then additional data could be requested.

The resulting review process typically resulted in a qualitative assessment in which the toxicity information was compared with the expected dietary exposure (usually a worst-case estimate) to determine if there were any risk concerns. If a substance had FDA approval(s) for various food additive uses, EPA generally considered that the uses regulated by FDA would result in greater dietary exposures than would typically occur as a result of its use as an inert ingredient in pesticide formulations. Accordingly, EPA would generally determine that no additional data were needed to support the inert ingredient use of the substance.

V. IMPACT of FQPA on the INERT REGULATORY PROGRAM

FQPA included specific amendments to FFDCA section 201(q)(1)) that defined an inert ingredient as a pesticide chemical. Thus, the FQPA standard of "reasonable certainty of no harm" applies to both active and inert ingredients when establishing a tolerance or tolerance exemption.

EPA's regulations at 40 CFR part 180 do not specify exactly what data must be submitted with a petition to establish a tolerance or an exemption from the requirement of a tolerance. Section 180.7(b) identifies in general terms the types of information needed for approval of a tolerance or tolerance exemption. Within this regulatory framework, EPA makes decisions about what data are needed on a chemical-by-chemical basis, and acquires them through either FFDCA or FIFRA. For pesticide chemicals currently subject to a tolerance or exemption, or contained in a registered pesticide product, EPA may require data pursuant to either FFDCA section 408(f)(1)(C) or FIFRA section 3(c)(2)(B).

In an application for registration under FIFRA of a pesticide product, EPA routinely requires submission of a comprehensive array of test data on the pesticide active ingredient (see 40 CFR part 158), which provide the basis for EPA to make the section 408 safety finding in regard to that active ingredient.

In the 1987 policy statement on inert ingredients discussed above, EPA identified a base set of data that it generally found sufficient to evaluate the risks of new inert ingredients, or new uses of existing inert ingredients. This policy statement stated that in its chemical-specific deliberations EPA could conclude that some or all of these studies are unnecessary, or might deem additional data necessary to fully assess the risks. Since the enactment of the FQPA, which amended both FFDCA and FIFRA, OPP has been advising persons seeking a tolerance exemption for an inert ingredient that the base set of data described in the 1987 policy statement is no longer appropriate since it did not include information on exposure beyond that in a pesticide product and limited data with respect to developmental and reproductive toxicity.

The only information in the1987 data set pertaining to exposure is the provision calling for a description of the expected use pattern for the proposed inert ingredient. The 1987 data set did not consider that most substances used as inert ingredients in pesticide products could be chemicals that are commonly used in other industries. The Agency needs information on exposures to the chemical substance from all other sources in order to assess the safety from "all other exposures for which there is reliable information," as required by FFDCA section 408.

Additionally, the Agency is required to assess the risk from pesticide residues in food to infants and children taking into account potential pre-and post-natal exposures, and completeness of the data with respect to exposure and toxicity for infants and children. The 1987 inerts policy requested the submission of only a single developmental toxicity study, and no reproductive toxicity study. A single developmental toxicity study is generally considered insufficient

information, especially when coupled with the lack of exposure information, to assess the special sensitivities of infants and children.

The 1987 base set of data is no longer appropriate; however, the 1987 inert ingredient policy also "categorized inert ingredients according to toxicity" by creating Lists 1, 2, 3, and 4. As previously explained List 4 was subdivided in 1989 to List 4A and 4B. These Lists remain in existence, continue to be used by the Agency, and will be updated.

VI. CONSIDERATIONS in DESIGN of a NEW APPROACH

One of the most significant challenges in implementing an effective and efficient regulatory program for inert ingredients is creating a review process that is protective of human health and the environment, but which also recognizes that a large percentage of inert ingredients are not, in fact, likely to be of significant toxicological concern. It would be a poor use of societal resources to routinely require the submission and governmental review of an estimated 12 million dollars worth of data (the estimated current cost of the 40 CFR Part 158 (food-use) data set) for every inert ingredient when the Agency's expectation is that on the order of 50% of inert ingredients would be of low or low/moderate risk. At the same time, EPA must be able to identify problematic inert ingredients and then have the resources to take appropriate action to reduce these risks.

In searching for options for modifying the current inerts review process to ensure compliance with FQPA, EPA considered whether it was appropriate to simply require a complete Part 158 data set to support the use of an inert ingredient in a pesticide. EPA examined the proposition that if a Part 158 data set was necessary to support decision-making on an active pesticide ingredient, then the same data set should also be necessary for the other ingredients in a pesticide formulation.

Inert ingredients are not intended to poison or repel pest organisms; therefore, with some exceptions, inert ingredients generally do not possess the same kind of biological activity as substances used as active ingredients in pesticides. Biologically active chemicals are those that are capable of altering an organism's biological processes. Many chemicals have such activity. Inert ingredients are not generally used for their biological activity *per se,* but are used in pesticide formulations primarily for their physical/chemical characteristics. Active ingredients, on the other hand, are intentionally used because of their ability to alter the biological processes in a manner that can significantly impact the target organism. The 40 CFR Part 158 data set was designed to define the characteristics of a substance that was already known or suspected of being biologically active, and thus suspected of being potentially hazardous to human health.

Generally when considering the term pesticide, one thinks of conventional pesticides that are intended to kill rodents, insects or weeds. It is reasonable to be concerned that a substance that can kill a complex biological system such as a rodent, insect or plant can also be potentially hazardous to human health. For example, it is no surprise that organophosphate pesticides (such as chlorpyrifos and diazinon) and carbamate insecticides (such as carbaryl) can interfere with the human nervous system. The 40 CFR Part 158 data requirements and the current paradigm for assessing "conventional pesticides" was created for conventional active ingredients. Registrants of active ingredients have the option of requesting waivers of data requirements that they believe to be inappropriate. Similarly, the existing Part 158 data requirements are not always necessary to assess the risk of the lower toxicity inert ingredients.

EPA also considered whether a complete Part 158 data set would be sufficient to support the safety findings required by FFDCA for inert ingredients. In evaluating this proposition, EPA found that, when outlining the data requirements for pesticide active ingredients, the assumption had been made that the only significant source of exposure to the pesticide would be through the use of the substance as an active ingredient in pesticides. At the time that Part 158 was promulgated in 1984, EPA was not explicitly required to consider non-pesticidal exposure sources in its risk assessments. Therefore, while the pesticidal exposures are well understood, EPA's data requirements in Part 158 do not routinely solicit or require information on the other non-pesticidal sources of exposure to those substances.

Finally, EPA considered the appropriateness of routinely requiring submission of a Part 158 data set rather than the use of existing data, to support an assessment of a substance proposed for use as an inert ingredient in pesticides. Given that many inert ingredients have a long history of use in non-pesticidal products, there are existing bodies of available information which may be able to provide a sufficient basis for supporting a safety finding for a low or low/moderate toxicity chemical. What would be the added value of new data, when existing information may be able to provide sufficient information to support a safety finding? Even if the existing information could not provide sufficient information, it may be possible that the existing information when combined with a limited number of additional studies could provide the quality and quantity of data to support a safety finding.

In establishing a policy of relying on the existing, available information for a low or low/moderate toxicity chemical, the Agency considered not only the cost of routinely generating and reviewing an extensive data set, but also the impact of this decision on the use of laboratory animals. While taking into consideration principles of sound science including the need to conduct scientifically sound pesticide chemical hazard/risk assessments, as well as the legal requirements of FIFRA and FFDCA to protect humans (including sensitive subpopulations) and the environment from unreasonable adverse effects of pesticides, the Agency remains committed to avoiding unneeded or duplicative animal testing.

Given the toxicity characteristics and readily available toxicity information on some inert ingredients, as well as the reality that the public could receive more value if the resources involved in the testing were applied to substances that posed the greater risks to human health or the environment, EPA believes that it does not necessarily need a 40 CFR Part 158 data set for all pesticide inert ingredients in order to make the safety findings prescribed in FIFRA and FFDCA.

VII. ADDITIONAL CONSIDERATION: ALTERNATIVE APPROACHES FOR DETERMINING DATA REQUIREMENTS USED by VARIOUS REGULATORY PROGRAMS

As part of the development of this approach, OPP also examined various regulatory systems elsewhere. OPP was particularly interested in understanding how other regulatory bodies dealt with similar circumstances; that is, how other regulatory bodies balanced the need for effective regulation with efficiency. OPP paid particular attention to tiered assessment methods, tiered data requirements, or other approaches used to determine data requirements.

Food and Drug Administration (FDA)

Some of the same substances used as inert ingredients in pesticide products are also considered by FDA under its administration of FFDCA. These substances may have uses as food additives (both direct and indirect), cosmetics, dietary supplements, human drugs, and color additives, as well as animal drugs and animal feed items–all of which are (to varying degrees) regulated by FDA.

Direct Food Additives: These are substances deliberately added to food to achieve a specific technical effect, such as emulsification or calorie reduction.

Since 1982, FDA has used the concept of tiered testing requirements to obtain information about the safety of direct food additives and color additives. The concept is based on the assumption that the degree of effort expended to reduce uncertainty about the safety of a direct food additive or color additive should relate in some logical way to the likelihood that use of the substance poses a health risk to the public.

The criteria used by FDA in its safety assessment of direct food additives and color additives are provided in an FDA Center for Food Safety and Applied Nutrition (CFSAN) document entitled "Toxicological Principles for the Safety Assessment of Direct Food Additives Used in Food." This document (often referred to as the "Redbook") sets out guidelines based on a system of tiered information recommendations for additives in food and describes how FDA determines which toxicity tests are recommended to assess the safety of direct food additives. The Redbook delineates the toxicology information deemed appropriate for assessing the safety of direct food additives and color additives. The FDA approach incorporates information about expected human exposure and chemical structure/activity relationships into initial "Concern Levels" for food and color additives used in food. The extent and type of toxicity testing recommended for direct food additives or color additives used in food will depend on the initial Concern Level to which that additive has been assigned and available information about the metabolism, chemical composition, and toxicity of the additive. Recommendations for minimum testing are associated with each Concern Level, and these recommendations reflect FDA's consensus that extensive toxicity testing should be reserved for additives with high

exposures and potentially reactive structures and for additives that induce adverse toxic effects at low doses or after short exposures

Indirect food additives: These are substances that may come into contact with food as part of packaging or processing equipment, but are not intended to be added directly to food. They are also known as food contact substances.

Historically, FDA has based its recommendations for toxicity data to support the safe use of indirect food additives on the estimated intake of these additives. As a general rule, higher estimated intakes of substances in the diet pose both an increased risk of toxicity and a wider range of potential toxic effects. Uses of a food contact substance that increase the cumulative estimated dietary intake (CEDI) to greater than 1 part per million (ppm) or, in the case of biocides, to greater than 200 parts per billion (ppb) are the levels at which FDA has historically requested more comprehensive toxicity testing in order to address a substance's potential to induce diverse toxic effects. To address the risk of these effects, FDA has asked for longer term toxicity studies and toxicity studies that measure a wider variety of toxic endpoints. FDA believes that uses of food contact substances that have the potential for inducing diverse toxic effects of consequence to human health generally require longer term and more specialized toxicity testing to support their safe use.

Cosmetic Regulation: FDA is only able to regulate cosmetics after products are released to the marketplace. Cosmetic ingredients, with the exception of color additives, are not reviewed or approved by FDA before they are sold to the public. FDA cannot require companies to do safety testing of their cosmetic products before marketing. If, however, the safety of a cosmetic product has not been substantiated, the product's label must read: "WARNING: The safety of this product has not been determined." FDA does not have the authority to require manufacturers to register their cosmetic establishments, file data on ingredients, or report cosmetic-related injuries.

Dietary Supplement Regulation: FDA regulates dietary supplements under a different set of regulations than those covering "conventional" foods and drug products. The dietary supplement manufacturer is responsible for ensuring that a dietary supplement is safe before it is marketed. FDA is responsible for taking action against any unsafe dietary supplement product after it reaches the market. Generally, manufacturers do not need to register with FDA or get FDA approval before producing or selling dietary supplements. Manufacturers must make sure that product label information is truthful and not misleading.

Human Drug Regulation: FDA evaluates drugs (including prescription drugs, over-the-counter drugs and generic drugs) under FFDCA to determine if the drug is safe and effective for its intended use, and that the established benefits of the drug outweigh its known risks.

Since 1938, every new drug has been the subject of an approved New Drug Application (NDA) before U.S. commercialization. The data gathered during the animal studies and human clinical trials of the Investigational New Drug phase become part of the application.

The inactive components of a drug, referred to by FDA as excipients, are also reviewed as part of the NDA review. If the excipient has been previously approved for use in another drug (FDA maintains a list of "approved" excipients), FDA will first determine if the use in the NDA results in any significant increase in exposure (particularly duration of exposure) to the excipient. If there is a significant increase in exposure, or if the excipient has not previously been approved, FDA will evaluate its safety in light of the proposed drug use. These safety evaluations are done on a case-by-case basis, with no specified toxicological testing requirements. FDA generally considers a weight of the evidence type approach when determining the need for additional toxicological testing of drug excipients.

Office of Pollution Prevention and Toxics: Premanufacturing Notice (PMN) Program

Under the Toxic Substances Control Act (TSCA) in order to require that testing be performed on a chemical, the Agency must either find that, among other things, the chemical "...may present an unreasonable risk to human health or the environment..." or "...is or will be produced in substantial quantities, and such substance either enters or may reasonably be anticipated to enter the environment in substantial quantities or there is or may be significant or substantial human exposure to the substance..." The latter finding has been termed an 'exposure-based finding' and allows EPA the option to require testing if certain production volume and exposure triggers are met.

Section 5 of TSCA does not require any toxicity testing for a new chemical prior to submission of a Premanufacture Notification (PMN), although if toxicity data are in the 'possession and control' of the submitter, these data must be presented at the time of the PMN submission. Since, in general, little or no data are received with a PMN, hazard assessments for the subject chemical depends heavily on models, structure-activity relationships (SAR) based on analogous chemicals, or data on the subject chemical retrieved from public databases or reference material. Using the available information, both human health and ecotoxicity concerns are identified. Levels of concern are generally described by terms such as high, moderate, or low. After the hazard assessment has been performed, then an exposure assessment, based upon the scenarios most appropriate to the chemical, is completed.

Almost 90 percent of the PMNs submitted to the program complete the review process without being restricted or regulated in any way. If the Agency determines that a new chemical substance may pose a risk to health or the environment, and lacks sufficient toxicological information; then, section 5(e) of TSCA allows EPA to issue an order requiring the PMN submitter to manufacture or import the new substance under specified conditions (risk-based consent order). The order may require development of additional test data as a pre-condition of its termination. In the absence of a risk finding and sufficient toxicological data, and faced with

the potential for substantial human or environmental exposure, section 5(e) of TSCA allows EPA to issue an order to collect data that will better characterize the substance's toxicity and risk (exposure-based consent order). In cases where the Agency determines that a new substance will present an unreasonable risk, section 5(f) of TSCA allows EPA to prohibit the manufacture, processing, or distribution in commerce of the substance.

Office of Pesticide Programs (OPP): Conventional Pesticide Active Ingredients

Historically, OPP's focus has been on conventional pesticide active ingredients which are generally synthetic/manufactured chemicals that directly kill or inactivate the pest. As discussed above, the Agency has presumed, when assessing the risk posed by an active ingredient in pesticides, that the pesticidal uses of the substance will account for virtually all exposures. Because of this presumption, the Agency has linked data requirements to the expected exposures associated with the various uses of a pesticide active ingredient. Accordingly, pesticide use patterns that result in pesticide residues in or on food trigger a requirement for data that show the effects of dietary exposures to the active ingredient (and its biologically significant degradates or metabolites). Pesticide use patterns that could result in residues in drinking water trigger requirement for data that show the likelihood of such occurrence. If these data show that the pesticide is capable of migrating into drinking water, the Agency requires additional data to further characterize this hazard. If the pesticide has uses in and around the home, then the Agency can also require additional data to further characterize this hazard.

Petitioners and registrants can also ask the Agency to waive data requirements that they believe are not necessary. The Agency examines the information submitted to support the waiver and determines whether to grant the request.

Office of Pesticide Programs (OPP): Biological Pesticides

Biological pesticides or biopesticides are almost exclusively derived from naturally occurring materials (animals, plants, bacteria, and certain minerals). Biopesticides are generally considered to be inherently less toxic to humans than conventional pesticides. Biopesticides are often effective in very small quantities and decompose quickly. Due to the relatively specific nature of their pesticidal effects, biopesticides generally affect only the target pest and closely related organisms.

Biopesticides include the following three categories: microbial, plant, and biochemical

- Microbial pesticides , which include a microorganism (e.g. a bacterium, fungus, virus, or protozoan) generally as the active ingredient.

- Plant-incorporated protectants which are pesticidal substances intended to be produced and used in a living plant and the genetic material necessary for the production of the pesticidal substance.

- Biochemical pesticides which are naturally occurring substances or synthetic compounds essentially identical to natural substances that control pests by non-toxic mechanisms. This would include substances such as insect sex pheromones that interfere with mating as well as various scented plant extracts that attract insect pests to traps.

Since biopesticides generally tend to pose lower risks to humans than conventional pesticides, the Agency generally requires much less data concerning human dietary toxicity and exposure to register a biopesticide than to register a conventional pesticide. Not only are the data requirements generally less extensive for biopesticides, but EPA can require different types of studies that target other potential types of risks. (See 40 CFR 158.65, 158.690, and 158.740)

Office of Pesticide Programs (OPP): Antimicrobial Pesticides

Antimicrobial pesticides, such as disinfectants and sanitizers, are defined in FIFRA section 2(mm)(1)(A) as pesticides that are intended to "(i) disinfect, sanitize, reduce, or mitigate growth or development of microbiological organisms; or (ii) protect inanimate objects, industrial processes or systems, surfaces, water, or other chemical substances from contamination, fouling, or deterioration caused by bacteria, viruses, fungi, protozoa, algae, or slime." FIFRA section 3(h)(3)(A)(ii)(III) requires that EPA "conform the degree and type of review to the risks and benefits presented by antimicrobial pesticides and the function of review under this Act, considering the use patterns of the product, toxicity, expected exposure and product type." Thus, EPA considers the need to ensure efficacy of public health pesticides when the pests are invisible disease-causing microbes. The data requirements for each antimicrobial use category are commensurate with the potential exposure and risks associated with that use pattern, including the need to demonstrate the effectiveness of the formulation with respect to controlling the public health pest. In some cases requirements are tiered so that higher exposures or higher risks require a second level of data. The amount and types of data required to support a use determines the level of detail and the complexity of the review process.

VIII. SHIFTING to a METHODOLOGY THAT SCREENS for LOWER TOXICITY

The methodology for determining the data needs, characterizing the hazard, and determining the risk of inert ingredients must be flexible enough to apply to a broad range of possible use patterns including those of conventional pesticides, biopesticides, and antimicrobial pesticides. EPA believes that a screening process that incorporates elements of a tiered data approach is appropriate due to the wide differences in toxicity among inert ingredients.

The terms "inert ingredient" and "active ingredient" as used under FIFRA refer to the function of the chemical substance within a particular pesticide product. There is no such functional distinction under the FFDCA. Under FFDCA, an inert ingredient is evaluated under the same standard as an active ingredient, that is, "a reasonable certainty of no harm." However, the statute does not stipulate that there is only one risk assessment approach that could be used by the Agency when making these assessments. Indeed, just as it would be inappropriate to require identical data sets for all ingredients in all pesticides (as discussed in Units VI and VII), the use of only one risk assessment approach would also be inappropriate. The Agency intends to use the methodology described in this paper for reassessing some of the 870 inert ingredient tolerance exemptions as required by FFDCA section 408(q) by the August 2006 deadline, as well as processing petitions for new inert ingredients for use in pesticide formulations for use on food or feed, and reviewing new inert ingredients proposed for non-food formulations.

FIFRA distinguishes active pesticide ingredients from other ingredients in the formulation. Active ingredients are always identified on the pesticide label. List 1 inert ingredients are listed as part of the formulation. But the identities of other inert ingredients in a pesticide formulation are not normally listed on the label. Therefore, as part of its review of an application for pesticide registration, the Agency must determine whether the ingredient listing on the product label is accurate. In distinguishing whether a pesticide ingredient should be regulated as an active ingredient or as an inert ingredient, the Agency considers information on the concentration, purpose, and mode of action of the ingredient in the formulation. This distinction must be made on a product-by-product basis since some substances are used as an active ingredient in one pesticide product and an inert ingredient in another pesticide product. The following are examples of chemicals, that have uses as both an active ingredient and an inert ingredient.

- Ethanol is a disinfectant and microbiocide (an active ingredient) at high concentrations. Ethanol is also a powerful solvent; therefore, a small amount of ethanol could be used to dissolve another chemical, which could then be added to the formulation. At much lower concentrations, ethanol cannot function as a disinfectant or microbiocide (an active ingredient), but does function as a solvent - an inert ingredient.

- FD&C Blue No. 1 is approved by FDA for use as a colorant in foods, drugs and cosmetics. As an inert ingredient it is used as a dye to color the pesticide product. It is also an active ingredient, an algicide. When added to water in a fish pond, the dye absorbs the light needed by the algae; and causes the algae to die. This is considered a pesticidal use, for which the dye is the active ingredient.

- Canola oil, which is also known as rapeseed oil, is a refined vegetable oil that can be used as an active ingredient to control insects in a wide variety of crops. Scientists believe that canola oil repels insects by altering the outer layer of the leaf surface or by acting as an insect irritant. Oils such as canola, however, can also be used as a surfactant (to modify the surface characteristics of a solution) in pesticide formulations. When used in this capacity, canola oil would be an inert, rather than an active, ingredient.

FIFRA also requires the Agency to determine whether a pesticide product as a whole, including the active ingredients and all other ingredients poses an unreasonable risk to man or the environment. FQPA amended FFDCA to stipulate that, when establishing tolerances or exemptions from the requirement of a tolerance for pesticide chemical residues, the Agency must be reasonably certain of no harm from exposures to pesticide chemical residues in or on food. A chemical substance's hazard characterization is a function of toxicity, not whether the chemical is considered to be an inert or an active ingredient.

The chemical's potential toxicity should drive the selection of data that will be needed to characterize the hazard rather than the chemical substance's classification as an active or inert ingredient in a pesticide product. For those low toxicity food-use pesticide chemicals for which only a minimum toxicology database is deemed necessary, a "reasonable certainty of no harm" finding could be accomplished in the qualitative sense, particularly for those pesticide chemicals for which an exemption from a tolerance would be granted.

OPP has always set different data requirements under FIFRA for broad categories of pesticides (e.g., antimicrobial public health pesticides, conventional pesticides, biopesticides). In regard to FFDCA data requirements, OPP has concluded that it is appropriate to make a similar distinction between chemical residues of high toxicity and those of low or low/moderate toxicity. OPP believes that this distinction is of far greater significance to dietary risk than the purely functional distinction between chemicals' roles as "inert" or "active" ingredients in any particular pesticide product, and that the data needed should reflect the expected risks. This methodology was originally developed for evaluating inert ingredients. However, under the appropriate circumstances, OPP proposes to use this methodology to establish exemptions from the requirement of a tolerance based on the toxicity of the chemical substance, not on its use as an inert or active ingredient.

IX. USE of EXISTING CHEMICAL INFORMATION/ DATA

In addition to relying on existing chemical information/data to make the initial Tier determinations, OPP intends to use existing chemical information/data in its efforts to make a confirmatory judgement concerning a chemical's low or low/moderate toxicity provided the information/data can provide sufficient, credible information to make a safety finding. As previously discussed, if the confirmatory judgement concerning a chemical substance's low or low/moderate toxicity cannot be made, then the use of this methodology is not appropriate. The determination as to whether or not the existing chemical information/data are acceptable for assessing the hazard of a particular chemical substance will be made by OPP on a chemical-by-chemical basis as part of the overall review and evaluation process of each chemical.

OPP has used and will continue to use this methodology on a chemical-by-chemical basis. But, even considering the pilot projects that have been undertaken by OPP that have included the search for and use of existing information/data, this is still the beginning stages of process development, and totally comprehensive guidance on the types and sources of information/data that could be used to make the confirmatory judgement concerning the low or low/moderate toxicity of a chemical is not possible at this time. However, OPP can provide some basic principles of data acceptability and a description of how OPP would attempt to locate existing, scientifically-valid data.

First of all, the information/data must be relevant. The types of information/data needed are those that address endpoints that are relevant to evaluating a chemical's toxicity and then performing a risk assessment. This would include ecotoxicity and human health effect endpoints, environmental fate endpoints and physical-chemical property endpoints.

Second, the information/data must be of sufficient quality and quantity. It must be credible, that is, scientifically valid. Generally, when evaluating active ingredients , the Agency has relied on data generated using the protocols given under the OPPTS Harmonized Test Guidelines. These guidelines contain many parameters of toxicity (e.g, studies that address human health endpoints would generally need to report the number of organisms tested, the dose/concentration levels used, the route/type of exposure, the duration of the exposure, the species tested, description of controls and statistical analysis). Conformance to these parameters result in studies which provide scientifically adequate data that can be used to determine a dose-response relationship, which is critical for performing a quantitative risk assessment.

Considering the considerable amount of testing that has been conducted on many chemicals, there could be existing information/data which may not have been generated in accordance with OPPTS test guidelines. However, many of these studies have been vetted in peer review or have undergone a formal review process. These vetted, peer-reviewed studies can significantly inform the risk assessment process for low or low/moderate toxicity chemicals.

Thus, in its review and evaluation process, OPP would focus on the credibility and scientific validity of the information/data, not on whether the existing information/data is a guideline study.

The data that would be most useful to OPP would be articles from peer-reviewed, internationally recognized journals. Generally, these articles would discuss studies that were conducted no longer than 10 years ago. (Note the 10-year time-frame is offered as a guideline: an older study could still provide valuable information.) It should be ascertained that the study would provide an appropriate amount of information on how the study was conducted, and what data were obtained, as well as the conclusions that were drawn. The Agency requires sufficient, credible information with which to make its decision, not an overwhelming amount of information.

There are numerous sources for locating existing studies and data. OPP is currently using a process of the following type when conducting searches to identify and locate existing chemical information/data.

OPP begins its search for chemical information/data with electronically searchable databases that can be accessed via government operated (.gov), publicly available websites. These databases contain inventories of scientifically peer-reviewed data on a large number of chemicals. The National Library of Medicine maintains such a database that can be accessed at: www.toxnet.nlm.nih.gov. This website contains links to HSDB (Hazardous Substances Data Bank), IRIS (Integrated Risk Information System), CCRIS (Chemical Carcinogenesis Research Information System), and GENE-TOX. All of these contain validated peer-reviewed data. Other databases also located at the National Library of Medicine can be found at www.nlm.nih.gov/. Careful consideration needs to given to the search terms used with a site such as NLM Gateway, otherwise hits on hundreds of journal articles are possible.

The National Toxicology Program (NTP) conducts chemical bioassays on a number of substances. Summary reports of the bioassays reviewed by NTP can be found at: ntp-server.niehs.nih.gov. The Agency for Toxic Substances and Disease Registry (ATSDR) produces "toxicological profiles" for certain hazardous substances which can be found at www.atsdr.cdc.gov/toxprofiles/. There is various information from OSHA/NIOSH (Occupational Safety and Health Administration/National Institute for Occupational Safety and Health), such as that on a Chemical Sampling Information Card or an International Safety Card. These can be found at www.cdc.gov/niosh/ipcsneng/neng0000.html and www.cdc.gov/niosh/npg/npg.html. The Firstgov website, www.firstgov.gov/, can also be used.

The International Agency for Research on Cancer (IARC) is part of the World Health Organization. The IARC evaluates chemical bioassays and the IARC website, www.iarc.fr/, contains summary reports of those bioassays reviewed by IARC.

Another source of information would be EPA's High Production Volume (HPV) Challenge Program which is part of the Agency's Office of Pollution Prevention and Toxics (OPPT) Chemical Right-to-Know Initiative. (www.epa.gov/chemrtk/volchall.htm) This voluntary program was developed to collect and make publicly available a baseline set of health and environmental data (hazard information) on the industrial chemicals that are the most widely used in the United States, i.e., those produced or imported into the U.S. in amounts greater than 1 million pounds per year. This baseline or screening data set is consistent with the international Organization for Economic Cooperation and Development (OECD) HPV SIDS Program, and represents an internationally agreed upon set of tests that can screen chemicals for potential hazards. Sponsors of HPV chemicals under the HPV Challenge Program have agreed to gather and assess the adequacy of existing information/studies and, if adequate information does not exist, to develop the needed data. The sponsors prepare robust summaries of the data (both existing and newly developed data), which are then posted on the Agency's ChemRTK Web Site.

Depending on the level of detail in the data summaries, the voluntarily submitted information could be useful to OPP's decision-making process. It is possible that some robust summaries could be used as is, or, in other cases, that the original study could be submitted to OPP for review and evaluation. The HPV Program has issued a guidance document "Determining the Adequacy of Existing Data" (www.epa.gov/chemrtk/datadfin.htm). This guidance document should be helpful to those wishing to submit data to OPP.

EPA's Voluntary Children's Chemical Evaluation Program (VCCEP) is also part of the Agency's Chemical Right-to-Know Initiative and will focus on industrial chemicals to which children are likely to be exposed. The goal of this voluntary program is to gather and/or develop both chemical hazard and exposure information that can then be carefully evaluated to ensure that children are adequately protected from potential risks associated with exposure to industrial and commercial chemicals. No submissions have yet been received; however, these submissions could also eventually provide information that could be useful to OPP's decision-making process.

EPA's TSCA Section 4 Testing Program addresses industrial chemicals and has required by rule the development of a range of health and environmental effects data on several hundred industrial chemicals. Full study reports are submitted to the Agency. Summaries of the testing results are posted on the Agency's website at www.epa.gov/opptintr/chemtest/4top.htm.

Generally, OPP would not attempt to search further than the above sources. However, there are other sources of information that could be used by a proponent of a tolerance exemption to locate and identify existing information/data which could then be provided to OPP. For example, there could be a scientific assessment that was performed by an expert panel. These could include assessments performed by various trade associations and documented in the form of a monograph, or a self-affirmed GRAS (generally recognized as safe) determination.

There are also evaluations that were performed by FDA to evaluate a dye or to affirm a GRAS substance. Many of these assessments are based on peer-reviewed data. However, FDA's GRAS determination relates to the use of a particular chemical substance in food, and can specify limitations on the food-use pattern. Additionally, FDA does not consider the possible presence of the chemical in drinking water, or in other products that can be used in and around the home, as EPA is required to do under FFDCA section 408. Under FIFRA, the Agency must also consider ecological effects of the chemical when sprayed on a agricultural field. Thus, the FDA GRAS determination can provide valuable information, which can then be supplemented by other existing, scientifically-valid information/data.

Most formulators of pesticide products purchase the chemical substances that are then incorporated into pesticide products. Therefore, another possible source of data is the manufacturer/supplier who could submit these data to OPP.

In conclusion, it should be remembered that those persons wishing to establish or maintain a tolerance or tolerance exemption have the responsibility of providing sufficient and adequate information, appropriate to conducting a hazard and risk assessment, to the Office of Pesticide Programs. In the absence of sufficient information to support an FFDCA section 408 safety determination, EPA may deny or revoke a tolerance or exemption from the requirement of a tolerance.

X. ROLE of EXPOSURE ASSESSMENT in this SCREENING/TIERED METHODOLOGY

This paper, up to this Unit, has focused on the role of the toxicity, the hazard assessment, of the chemical substance. Toxicity is the driving force in determining tier placement. However, risk, the basis for the FQPA safety finding, is a function of both hazard and exposure. The exposure assessment can potentially impact the type of risk assessment to be performed. It is also possible that chemical substances of low toxicity could need submission of additional toxicity and/or exposure data if the exposure assessment indicated the potential for extremely high exposure.

In the typical human health risk assessment performed by the Office of Pesticide Programs for a conventional active ingredient the methodology for performing the exposure assessment relies on an extensive data set and modeling. Exposure assessments for dietary, drinking water, residential, and occupational exposures can be performed in a tiered fashion to refine the exposure estimates. Performance of probabilistic (Monte Carlo) simulations for dietary exposure are routinely performed. The different kinds of exposures for each active ingredient are well-documented. Each new use of the active ingredient is documented in a new risk assessment to make sure that the Agency's level of concern is not exceeded and that the FQPA safety finding can continue to be made. The result of the quantified risk assessment is that tolerances with specific numerical limitations are established under FFDCA.

This screening/tiered methodology is different, because tolerance exemptions are different from numerical tolerances. For the low or low/moderate toxicity substances that will be considered, the intent is to determine whether tolerance exemptions are appropriate. Establishment of a tolerance exemption can be unlimited (no restrictions), or can have some specific types of limitations such as indicating that the chemical substance would only be used as a surfactant or a limitation on the percent of the chemical substance in the formulation. Once a tolerance exemption has been established, there is no limitation on the amount of residues of the chemical substance that could be present in food or feed, and the chemical substance has the potential to be used in any pesticide product, applied to any crop, at any percent in the formulated pesticide product (subject only to the limitations as discussed above, if present). Thus, as pesticide products exit and enter the market place, the use patterns for any particular chemical substance with a tolerance exemption can change.

Given this potential for shifting use patterns, it is necessary to examine a wide-range of use patterns. The need to assume wide-ranging, constantly-changing exposure scenarios (instead of having specific, well-defined exposures) for tolerance exemptions necessitates a unique approach for both dietary (food and drinking water) exposures and residential exposures. Rather than conducting a separate exposure assessment for every conceivable scenario, representative exposure estimates will be used to account for a wide range of potential uses.

Under this methodology exposure assessments will be conducted in either a qualitative or quantitative manner. A qualitative exposure assessment would yield a qualitative risk assessment, that would discuss both the potential pesticidal exposures and the non-pesticidal exposures, as can best be determined.

Risk assessments for most Tier 1 chemical substances would be performed in a qualitative manner. The risk assessment would focus on the low toxicity of the chemical substance which would be combined in a qualitative manner with the understanding of the exposure assessment. The combination of low toxicity even after considering the possibility of extensive exposures resulting from a wide-ranging exposure pattern would generally result in a low risk concern for the chemical substance. However, if concerns were identified during the performance of the qualitative risk assessment, there would be the option of switching to a quantitative risk assessment.

Under this screening/tiered methodology, quantitative risk assessments would focus on bounding the wide-ranging exposure pattern. The bounding level approach is based on all the practices currently used by OPP's exposure assessors. However, instead of using inputs defined by the known/existing use practices, the inputs for this screening/tiered methodology will be based on conservative estimates of the potential high-end exposures that could occur. Bounding level exposure estimates would be generated for dietary (food and drinking water) and residential (dermal and inhalation) exposures.

OPP has already developed one bounding level exposure estimate for dietary exposure resulting from pre-harvest uses of a chemical substance. The modeling assumed that the "chemical" would be used on all crops, that 100% of all crops would be treated with the "chemical", that residue levels could be as high as the highest established tolerance levels for each commodity, and that secondary residues in meat, milk, poultry and eggs could occur. These inputs were then combined with the consumption information used in all OPP dietary modeling. Dietary exposure estimates were then generated for acute and chronic scenarios for various population subgroups. At this time, additional bounding level exposure estimates are being developed for other routes of exposure.

The resulting exposure estimates would be compared to the hazard data to determine whether any risk concerns exist. This qualitative comparison would not involve mathematical operations to add up the exposures. It would not be scientifically valid to try to quantify risk based on these bounding level exposure assessments because their conservative assumptions would overstate the risk. If, based on the qualitative comparison, there are no risk concerns, then no further assessment would be conducted, and the tolerance exemption would be established.

However, it is always possible during the performance of either a qualitative or quantitative risk assessment that risk concerns could be identified. Once these concerns have been identified, then under this methodology there are various actions that could be taken. As previously stated, the determination could be made to shift from a qualitative to a quantitative

risk assessment, or there could be a request for information to better characterize either the hazard or the exposure. Under FFDCA, to establish either a tolerance or tolerance exemption, the Agency must find that "there is a reasonable certainty of no harm". In the absence of sufficient information to support an FFDCA section 408 safety determination, EPA may deny or revoke a tolerance or exemption from the requirement of a tolerance.

Under this methodology, consideration will also be given to ecotoxicity and worker exposures. These exposures are not expressly considered when establishing tolerance exemptions under FFDCA section 408, but are evaluated as part of the pesticide product registration process under FIFRA. Any substance-specific concerns for potential adverse effects to nontarget organisms or to those persons who may be involved in the application of pesticides will be flagged for further consideration as part of the product registration requests as well as being considered during List reclassification determinations.

As OPP reassesses the 870 inert ingredient tolerance exemptions List reclassifications are also being performed (see Unit IV for List descriptions). All tolerance exemptions that have been reassessed are by definition List 4. However, OPP must distinguish between a List 4A and List 4B inert ingredient. The determination that a chemical is List 4A would be based on a recognition of the overall safety of the chemical (such as very low toxicity or practically non-toxic) considering the widely available information on the chemical's known properties, and a history of safe use under reasonable circumstances. List 4A substances are recognized as safe for use in all pesticide products subject only to good agricultural practices or good manufacturing practices. Classification as a List 4A inert ingredient is a high standard to meet. As an example, substances of high acute toxicity are usually not considered for classification to List 4A. The critical distinction between List 4A minimal risk substances and other substances, is that the Agency does not define how, where, when or in what manner the substance can be used. Any reasonably foreseeable use of these substances is not expected to present a risk to humans. Accordingly, there should not be any unreasonable adverse effects from the inclusion of a List 4A substance in a pesticide product to the person applying a pesticide product in and around their home, to a child in a day-care center, or when ingesting a food commodity that has been treated. In making a List 4A reclassification OPP will consider not only the exposures that are assessed under a FFDCA section 408 decision, but also potential ecotoxicity and worker exposure concerns.

For all Tier 1 and Tier 2 chemical substances, a quantitative worker exposure assessment, as performed in the active ingredient higher toxicity paradigm, would not be performed. However, as part of the FIFRA registration process the Agency requires the submission of six acute end-product toxicity tests. These tests are the basis for labeling language for the first aid statement, determine the types of protective equipment such as gloves and respirators, and affect the decision on whether or not the product can be used in and around the home. This approach to worker protection is only possible due to the lower toxicity of the chemical substances that are considered under this screening/tiered methodology.

XI. COORDINATION with OTHER DATA GENERATION PROGRAMS at EPA

It is entirely possible that a chemical substance could be regulated by the Office of Pesticide Programs (OPP) as a pesticide chemical, as either an inert or an active ingredient, and that same chemical could also be regulated by the Office of Pollution, Prevention and Toxics (OPPT) under the New Chemicals Program (NCP) or as an existing chemical subject to TSCA Section 4 test rules. Or, the chemical substance could be the focus of data collection/development efforts such as the High Production Volume (HPV) Challenge Program or the Voluntary Children's Chemical Evaluation Program (VCCEP). These are very different Programs.

- OPP is a regulatory program that operates under FFDCA and FIFRA. Without EPA's prior approval, a pesticide product cannot be offered for sale or distribution in the United States. Registrants of pesticide products must submit the necessary data to maintain their registration to OPP for review and evaluation. There can be statutory deadlines.

- The NCP (TSCA section 5 premanufacture notification program) regulates the manufacture of new industrial chemicals. There are no pre-set data requirements; therefore, the program relies heavily on the use of SAR (structure-activity-relationship) to assess human and environmental toxicity. The NCP has successfully used SAR to assess over 35,000 chemical substances since its inception.

- EPA's TSCA Section 4 Testing Program addresses industrial chemicals and has required by rule the development of a range of health and environmental effects data on several hundred industrial chemicals. Full study reports are submitted to the Agency. Summaries of the testing results are posted on the Agency's website.

- HPV is a voluntary program that was designed with significant stakeholder input. Sponsors of HPV chemicals under the HPV Challenge Program have agreed to gather and assess the adequacy of existing information/studies and, if adequate information does not exist, to develop the needed data. Robust summaries and test plans are prepared by the sponsors and are posted on the Agency's website. The adequacy of the data is determined based on robust summaries of key studies for the various endpoints.

- VCCEP is also a voluntary program whose goal is to gather and/or develop both chemical hazard and exposure information that can then be carefully evaluated to ensure that children are adequately protected from potential risks. VCCEP was designed with significant stakeholder participation.

There are also programmatic similarities. The common theme among these Programs is the critical need to collect/develop data. Each of the Programs has a tiered approach to characterizing its data needs. There is a functional similarity between OPP's Tier 2 and with HPV's and VCCEP's Tier 1. (See Appendix) OPP's Tier 3 is a very extensive data set that can

have similarities to a TSCA section 4 test rule. OPP and OPPT will coordinate, as best possible, to assure that the three programs operate efficiently and productively while supporting each others efforts. However, it is entirely possible that the same or similar data could be evaluated in a somewhat different manner under these different Programs.

Coordination could involve the following types of scenarios:

Currently VCCEP has a pilot program to assess 23 chemicals. There is overlap with chemicals that are used in pesticide products. However, in most cases, the overlapping VCCEP-sponsored chemicals are those inert ingredients of potentially higher toxicity and therefore would not be assessed using OPP's screening/tiered methodology described herein. Pesticide formulators are encouraged to work with the manufacturer/supplier of the VCCEP chemicals that are incorporated in their formulation to provide input for preparation of the VCCEP exposure profiles. Since some of the VCCEP chemicals are List 2 inert ingredients, OPP does intend to issue Data Call-In (DCI) Notices to pesticide registrants who incorporate these List 2 inert ingredients into their products. As a result of their VCCEP sponsorship, the manufacturers/suppliers would have already identified and/or generated some of the data required under the DCI. These data could be reviewed and evaluated, and then be used in a risk assessment to support OPP's regulatory decision.

Another area of overlap, that has already occurred is with the HPV Program; some chemicals sponsored under HPV are also used as either inert or active ingredients in pesticide products. In one case the HPV robust summaries had been recently posted on the internet. A comparison of the robust summaries with the data submitted to OPP indicated for the most part that it was the same data, and there was general agreement on the selection of doses and endpoints in the various studies. In another case, OPP was able to review the robust summaries submitted to OPPT before posting. There was a difference in the data submitted to OPP and the robust summaries submitted to OPPT. OPP's data were conducted on the chemical of interest and its calcium and sodium salts. The robust summaries were conducted on the chemical of interest and two derivatives. Also present was a rationale including metabolic arguments as to the appropriateness of the use of the derivatives. OPP is moving forward on its regulatory decision based on the data submitted to OPP, with consideration of the information submitted to OPPT. OPP's regulatory decision is based on the information available at the time the decision is made. However, any submission of data as part of the HPV Challenge Program may, at any time in the future, be used by OPP to revise or update any decision as deemed necessary and appropriate. OPP and OPPT intend to coordinate, as appropriate, to keep each other apprized of any new data submitted and in particular the status of any assessments of overlapping chemicals in their respective Programs.

OPP and OPPT staff will also coordinate on development of methodologies for assessing exposure and on common documentation. Currently submissions of data to OPP are the studies. OPPT receives full studies under its regulatory Programs. However, robust summaries are

submitted to some OPPT Programs. Those persons submitting data to OPP for chemicals that are also sponsored under HPV or VCCEP are encouraged to also submit robust summaries of the data to OPPT.

For chemicals of lower toxicity that can be appropriately addressed under this screening/tiered methodology, OPP anticipates in many cases, that the data submitted voluntarily to the HPV or VCCEP Programs could significantly inform its decisions. However, if a chemical is also used as a pesticide inert ingredient, and more specifically is on List 1 or List 2, the Agency would like to clearly articulate that the data set that OPP would seek through a FIFRA DCI, would require registrants to generate an extensive data set specifically designed and proven over time to provide the appropriate data for assessing human health risk as required by the FQPA amendments to FIFRA and FFDCA. Although data satisfying the FIFRA DCI would generally meet the criteria of the HPV Challenge Program and the VCEEP Program, obtaining the baseline data set asked for under the HPV Challenge Program or the VCCEP Program would not be expected to satisfy a FIFRA DCI issued for a List 1 or List 2 pesticide inert ingredient.

XII. PRELIMINARY TIER DETERMINATION

The methodology currently being used by OPP is a screening process that incorporates elements of a tiered data approach. EPA tiers many of its data requirements. Under most tiered systems, the decision to continue to test the substance is based on the results of a previous tier of studies. However, given that this methodology is also a screening process, the tiered approach works in a somewhat different manner by immediately placing the chemical substance in the most appropriate tier.

It should be noted that the Agency's tier determination begins in a preliminary manner, focusing on the toxicity, the hazard characterization, of the chemical substance and an understanding of the types of assessments (qualitative or quantitative) possible for each tier. As the existing, scientifically-valid information/data on a particular chemical substance is reviewed and evaluated, the Agency may revise its tier determination.

OPP's preliminary tier determination is based on the available information on the chemical substances' potential toxicity. This can include not only the existing, scientifically-valid information/data but also a judgement made by OPP based on structural similarities and chemical families and categories, such as, alcohols or fatty acids.

The Tiers are briefly described below:

Tier 1a: Chemical substances that can be assessed under this tier would be those substances with a long history of safe usage. They are considered to be of low toxicity, and therefore even considering a wide-ranging exposure pattern would also be of low risk concern. It is anticipated that the rationale and justification confirming the low toxicity for these chemicals could be extremely limited and would consist of commonly or readily available knowledge on the lack of toxicity; therefore, Tier 1a chemical substances would not require submission of any toxicological data.

Tier 1b: Chemical substances that can be assessed under this tier would include chemicals for which some information/data would be necessary to make the confirmatory judgement concerning the substances' low or low/moderate toxicity. Confirmation of the low or low/moderate toxicity of substances in Tier 1b would be based upon information such as a review of existing, scientifically valid information/data (see Unit IX) and/or a SAR (structure-activity-relationship) assessment. The qualitative exposure and risk assessment for these chemicals would be more than that needed for a Tier 1a rationale and justification. However, it is also possible that a quantitative risk assessment similar to that performed for Tier 2 may be performed.

Tier 2: Generally, Tier 2 chemical substances would be those for which OPP does not have and could not locate sufficient existing, scientifically-valid information/data to assess a chemical substance's toxicity. If the toxicity of the chemical cannot be determined, a Tier 1 determination

is not possible. For these Tier 2 chemical substances, OPP would request the submission of a limited data set to characterize the hazard of the substance. The data would consist of a unique data set - the Tier 2 data set - which would have similarities to the internationally recognized OECD screening information data set (SIDS). (see the Appendix) The Tier 2 hazard assessment would integrate the results of the submitted studies, a SAR assessment, and any existing, scientifically valid data (if available). Generally, Tier 2 exposure and risk assessments will be quantitative.

Tier 3: OPP would request for Tier 3 chemical substances the submission of a complete (food-use) 40 CFR Part 158 database, that is, a data set comparable to the data required to evaluate a conventional active ingredient intended for food use. Under Tier 3, List 1 and some List 2 inert ingredients would be evaluated in a similar manner to that of an active ingredient. These are chemicals that EPA suspects may pose significant risks, such as endocrine disruption, carcinogenicity, neurotoxicity, developmental and reproductive effects, ecotoxicity, persistence/bioaccumulation and/or significant dermal penetration.

In summary, the preliminary tier determination would be based on the available information. During a chemical's review and evaluation, and as additional information is received, the Agency can revise the tier determination either up or down. Thus, it is possible that a preliminary Tier 1b determination could go to Tier 2, or the reverse.

The amount and quality of the data required to establish or reassess a tolerance exemption increases as the level of toxicity increases. The intent of this screening process is not only to assure that each chemical is adequately assessed, but also to focus the Agency's resources on those chemicals of potentially higher toxicity and therefore potentially higher risk. Under this methodology OPP anticipates needing the complete 40 CFR Part 158 data set only for those chemical substances of significant toxicological concern such as List 1 or some List 2 inert ingredients. However, this screening/tiered methodology will provide sufficient information to allow the Agency to distinguish the lower toxicity chemicals from the higher toxicity chemicals as well as provide sufficient information for the characterization and assessment of lower toxicity chemicals.

XIII. EXAMPLES of TIER 1a and 1b ASSIGNMENTS for INERT INGREDIENTS

Tiers 1a and 1b would make use of existing information to make a confirmatory judgement concerning a chemical substance's low or low/moderate toxicity, and therefore even considering a wide-ranging exposure pattern these chemical substances would also be of low risk concern. OPP would use the existing, scientifically valid information/data to approve the use of these substances in a pesticide product. However, if the information is insufficient to make the confirmatory judgement that a substance has little or no toxicity and that aggregate exposures to such substance would not result in unacceptable risk, then the Tier 1a or 1b determination would be inappropriate. The preliminary Tier determination would be changed to Tier 2.

Tier 1a:

Inert ingredients that can be assessed under this tier would be those substances with a long history of safe usage. They are considered to be of low toxicity, and therefore even considering a wide-ranging exposure pattern would also be of low risk concern. Tier 1a substances would not require submission of any toxicological data. It is anticipated that the rationale and justification confirming the low toxicity for these chemicals could be extremely limited and would consist of commonly or readily available knowledge on the lack of toxicity.

Tier 1a risk assessments would be qualitative, drawing primarily on the substances' long history of safe use, to support establishing unlimited tolerance exemptions. In fact, non-pesticidal exposures to many of these materials may be frequent and at significantly higher levels than would occur as a result of pesticidal use. The safety finding would also be based on low risk, and usually allow for establishing unlimited tolerance exemptions.

Examples of chemical substances that are currently considered to be likely candidates for Tier 1a, that is, those chemical substances that could receive a preliminary Tier 1a determination, are described below:

- Commonly consumed food items (excluding known allergens): These are necessary to supply nutrition and there is a long history of safe use.

- Animal feed items: These items have been fed to animals without any evidence of ill effects. Examples of such materials would include corn cobs, and orange pulp/peel. Humans have safely consumed meat, milk, poultry and eggs produced by such animals.

- Weathered rocks and minerals, including silicates and oxides: These are the materials in and of the earth in which we grow our food. Examples of such materials would include sand and limestone. There is, thus, a long history of human exposure to these substances, including inadvertent dietary exposure.

- Polymers that conform to the criteria specified in the TSCA polymer exemption (40 CFR

723.250): OPPT reviewed over 12,000 polymer applications to determine these criteria which identify polymers of minimal toxicological concern.

- Inert gases (argon and helium): These gases are chemically inert. There are no known or suspected adverse effects. Pesticidal use of these substances is unlikely to significantly add to exposures from existing sources.

- Atmospheric gases (nitrogen and carbon dioxide): These are the gases that are present in the atmosphere that we breathe.

Tier 1b:

Inert ingredients that can be assessed under this tier would include chemical substances for which some data/information would be necessary to make a confirmatory judgement concerning the substances' low or low/moderate toxicity. It is anticipated that the qualitative risk assessment for these chemicals would be more than that needed for a Tier 1a rationale and justification. The kinds and types of data to make this low toxicity confirmatory judgement would vary from chemical to chemical. Approval of substances in Tier 1b would be based upon information such as a review of existing, scientifically valid data, and/or a SAR assessment, rather than based on the submission of new studies. Use of surrogate data may be acceptable to make the confirmatory judgement concerning the chemical substances' low or low/moderate toxicity. Most Tier 1b risk assessments would be conducted in a qualitative manner assuming wide-ranging exposure, although quantitative risk assessments could also be performed. OPP anticipates that the FFDCA section 408 safety finding would also be based on low or low/moderate toxicity with resultant low risk, and usually allow for establishing unlimited tolerance exemptions, although OPP may impose limitations on the tolerance exemption, if appropriate.

Examples of chemical substances that are currently considered to be likely candidates for Tier 1b, that is, those chemical substances that could receive a preliminary Tier 1b determination, are described below:

- FDA-approved food dyes: FDA has reviewed and evaluated the available data to support the use of Food, Drug, & Cosmetic (FD&C) dyes and Drug & Cosmetic (D&C) dyes. The exposure from the uses regulated by FDA should significantly exceed the exposures from pesticidal uses, i.e., the uses regulated by EPA.

- Known food allergens: These would include peanuts, tree nuts, milk, soybeans, eggs, fish, crustacea, and wheat. Various factors such as restrictions on post-harvest applications or information on the environmental degradation/metabolism of the allergen may enable the Agency to make a determination of safety by preventing or mitigating dietary exposure from the pesticidal use.
- Naturally occurring materials (such as humic acid) that are ubiquitous in the environment,

but are sometimes a highly refined version of the material or a synthetic compound essentially identical to the naturally occurring material: Exposure to the natural material is already occurring. However, if it is not possible to make the confirmatory judgement concerning the low toxicity of the synthetic or highly refined material based on a factor such as a long history of safe usage, then the use must be supported by data to assure that the chemical has little or no toxicity.

- Chemicals that are part of the normal metabolic processes that occur in the human body: This would include intermediates of carbohydrate metabolism, such as the citric acid (Krebs) cycle, and intermediates of lipid metabolism, such as lecithin. (This could also include salts of such chemicals.) Other possible metabolic processes could include formation of lactic acid from glucose, and formation of the non-essential amino acids that are synthesized by the human body: The assessment would include a discussion of the metabolic process and an evaluation of the existing, scientifically valid data.

- Essential amino acids (those not manufactured by the body) and some vitamins: The assessment would include a discussion of the metabolic process, an evaluation of the existing, scientifically valid data, and information on the existing non-pesticidal exposures.

- Natural fatty acids: These are long hydrocarbon chains that are attached to a carboxyl group (-COOH) and are formed during digestion of dietary fat. Fatty acids are transported from the gut into the blood stream and are also released from adipose tissue when fat is metabolized in the body. The assessment would include a discussion of the metabolic process, and an evaluation of the existing, scientifically valid data.

- Derivatives of natural fatty acids that may be considered are:
  - Fatty acid esters that occur when the fatty acid joins with another hydrocarbon chain (fatty acid chain-COO-R2)
  - Mono-, di-, and triacyl glycerols (also known as triglycerides). One, two, or three fatty acids are joined (through an ester linkage) to glycerol (an alcohol)
  - Salts of fatty acids

- Modifications of simple and complex carbohydrates: The assessment would include a SAR assessment.

- Gums (many are derived from plants, seaweed or algae): An evaluation of the existing, scientifically valid data would be necessary to make the confirmatory judgement that little or no toxicity is associated with exposure to these substances.

- Waxes: These are water-insoluble solid esters of higher fatty acids with long-chain fatty alcohols and generally have minimal to no dermal penetration. The assessment would include an evaluation of the existing, scientifically valid data and/or a SAR assessment to

make the confirmatory judgement that little or no toxicity is associated with exposure to these substances.

- Common mineral acids: These could include hydrochloric, sulfuric, sulfurous, carbonic, nitric, nitrous, phosphoric, phosphorous, hydrogen bromide, and hydrogen iodide. Existing, scientifically valid data should supply sufficient information to characterize the toxicity of these acids. Most acids could not be considered as low toxicity substances; however, these acids are usually used in pesticide products to adjust the pH of the formulated product. Given the small amounts that are used, the resultant risk should be low.

- Common hydroxides: These could include sodium, potassium, and calcium hydroxide. Existing, scientifically valid data should supply sufficient information to characterize the toxicity of these bases. Most bases could not be considered as low toxicity substances; however, these bases are usually used in pesticide products to adjust the pH of the formulated product. Given the small amounts that are used, the resultant risk should be low.

- Salts of certain inorganic acids and bases: This could include various salts such as ammonium, sodium, potassium, calcium, magnesium, zinc, iron, barium, or aluminum, but would not include salts such as cadmium or chromium. The assessment would include an evaluation of existing, scientifically valid data to demonstrate that little or no toxicity is associated with exposure to these substances. A SAR assessment may be necessary for some of the salts to assess ecotoxicity concerns.

- Aliphatic acids (RCOOH), alcohols (ROH), aldehydes (R-CO-H), (R1-COO-R2), and ketones (R1-CO-R2): The C range - the length of the hydrocarbon chain - would need to be determined. Some of these chemicals have been approved by FDA as GRAS or as direct food additives. The assessment would include an evaluation of existing, scientifically valid data and/or a SAR assessment to make the confirmatory judgement that little toxicity is associated with exposure to these substances.

- Rosins: These are the materials left after turpentine is removed from tree resins. The assessment would include an evaluation of existing, scientifically valid data and/or a SAR assessment to make the confirmatory judgement that little or no toxicity is associated with exposure to these substances.

- Lignins: These are derived from wood. The assessment would include an evaluation of existing, scientifically valid data and/or a SAR assessment to make the confirmatory judgement that little or no toxicity is associated with exposure to these substances.

- Cellulose: This is the major complex carbohydrate in plants. Cellulose, *per se*, may actually be Tier 1a; however, modifications of cellulose are more likely to be Tier 1b. The assessment would include a SAR assessment.

- Flower and vegetable oils/essential oils: These are natural components of plants that provide distinctive odor or flavor. For some of these oils, an evaluation of existing, scientifically valid data and/or a SAR assessment could be used to make the confirmatory judgement that little or no toxicity is associated with exposure to these substances. For other substances, the safety finding would acknowledge the use pattern, which is a low percentage of most formulations. Given the small amounts that are needed to provide the distinctive odor or flavor, the resultant risk should be low.

- Chemicals for which a scientific assessment already has been performed by an expert panel: These assessments can be documented in the form of a monograph, a self-affirmed GRAS determination, or an FDA evaluation. The Agency would conduct a streamlined review of the work of the panel to validate the panel's review, to understand and evaluate the differences in the use patterns, and to locate the additional information necessary to make the safety finding.

XIV. DESCRIPTION of TIER 2 ASSIGNMENTS

Chemical substances that cannot be readily assigned to Tier 1 (see Unit XIII) or Tier 3 (see Unit XV) would be initially assigned to Tier 2. If the confirmatory judgement cannot be made that a chemical substance has little or no toxicity, then a minimum data set to characterize the toxicity would be needed to evaluate such substances. This data would consist of a "screening" data set which would have similarities to the internationally recognized SIDS data set (see the Appendix).

XV. EXAMPLES of TIER 3 ASSIGNMENTS

For substances that are known or suspected of having significant toxicity, OPP anticipates that it would not be able to make the section 408 safety finding without a complete (food-use) Part 158 database. Such substances would be evaluated in a manner substantially similar to the approach for active ingredients in conventional pesticides, i.e. a quantified risk assessment considering aggregate exposures to determine if the risk exceeds the Agency's level of concern. Generally, these are chemicals for which the Agency has toxicological concerns such as endocrine disruption, carcinogenicity, developmental and reproductive effects, ecotoxicity, persistence/bioaccumulation and/or significant dermal penetration. These chemicals may have already been classified as List 1 "inerts of toxicological concern" or List 2 "potentially toxic inerts/high priority for testing". Usually, registrants whose products contain Tier 3 chemicals would be required to provide these data via a FIFRA section 3(c)(2)(B) Data Call-In (DCI) Notice.

Examples of chemical substances that might have preliminary Tier 3 determinations are described below:

- Phthalates are possible endocrine disrupters, and some have been evaluated by the National Toxicology Program for developmental/reproductive effects.

- Petroleum hydrocarbons are currently being evaluated by the Agency. Approximately 110 chemicals have been identified that are currently used in pesticide products. These chemicals would be grouped and a representative chemical(s) would be selected for each group. It is expected that these chemicals would be referred to the Inert Ingredient Focus Group (see Unit XVIII) before the DCI is issued to determine the data requirements.

- Preservatives (usually referred to as "in-can" preservatives as they protect the formulated product from microbial degradation before use) are oftentimes active ingredients. Many of the active ingredients used as in-can preservatives have only been registered for non-food uses, whereas the inert ingredient use could include use on food-crops.

- Chemicals with significant dermal absorption can carry the active ingredient in an unpredictable manner into workers' bodies (impacting the worker assessment), and plants and animals tissues (impacting tolerances). An example would be dimethyl sulfoxide (DMSO).

- Chemicals, such as herbicide safeners (which increase the tolerance of the desired crop to the herbicide). Many of these safeners are structurally related to and have similarities in biological activity to that of an active ingredient.

- Chemicals that are structurally similar to chemicals of toxicological concern

- Ethylene glycol ethers, especially short chain ethylene glycol ethers, are developmental and reproductive toxicants.

XVI. WEIGHT-of-the-EVIDENCE EVALUATION for CONDUCTING RISK ASSESSMENTS for TIER 1b and TIER 2 CHEMICALS

The ordinary process for assessing the dietary risks of pesticide active ingredients entails extensive data review and evaluation, multiple peer-reviews, and much documentation. EPA believes the decision process for low or low/moderate risk substances can be accomplished in a simpler, less intensive manner, and therefore has been exploring the use of a streamlined process that would reduce the extent of review, consultation and documentation needed to support such a risk assessment. At this time, OPP anticipates that Tier 1b and Tier 2 chemicals will be reviewed as described below:

Tier 1b

For a Tier 1b chemical, an evaluation of existing, scientifically valid data and/or the SAR assessment (described below) may be the only information considered by OPP. The information must provide a sufficient basis to make a confirmatory judgement on the low or low/moderate toxicity of the chemical substance. Aggregate exposure will be considered qualitatively. If the information is not sufficient, to support a reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, then the Tier determination would be changed to Tier 2.

Tier 2

Review and evaluation of Tier 2 chemicals would integrate a body of evidence that includes (1) a SAR (structure-activity-relationship) assessment, (2) an evaluation of existing, scientifically-valid information/data, and (3) the Tier 2 screening data set. Based upon these three sources of information OPP will determine whether the chemical substance meets the statutory criteria for a tolerance exemption. If the Agency does not in its review and evaluation identify any effects of concern, then it should be possible to establish or reassess a tolerance exemption for the chemical. However, if an effect of concern is noted during the review and evaluation process then additional targeted testing related to that effect would be requested or the chemical could be taken to Tier 3.

The Structure-Activity-Relationship (SAR) Assessments

There are various SAR assessment processes. The one described below was developed by OPPT as a tool for quickly assessing and predicting toxicity and environmental fate in the absence of chemical-specific data. OPPT scientists assess a chemical's structural similarity to chemicals for which data are available. For human health, this process can be used to assess absorption and metabolism, mutagenicity, carcinogenicity, developmental and reproductive effects, neurotoxicity, systemic effects, immunotoxicity, and sensitization and irritation. This is generally performed as a qualitative assessment; although, if a robust data base were available on an analogous chemical, an endpoint would be chosen by OPPT and a quantitative risk assessment

conducted. OPPT also performs an ecotoxicity and environmental fate assessment often using modeling data. In performing these assessments, OPPT assesses specific use patterns based on information supplied by the submitter as well as OPPT's professional judgement of future potential exposures.

The reliability of this approach as a method of assessing potential human and environmental risks has been examined in the Project on the Evaluation of (Quantitative) Structure Activity Relationships (EPA 743-R-94-001), conducted in cooperation with the European Union (EU). Given only chemical structure information, OPPT assessed 140 chemicals using their SAR assessment process. The results of their assessments were then compared to the "base set" data that the EU had received on each chemical. The results indicated that the SAR assessments were "on target" 90% of the time for aquatic toxicity, and roughly 80% of the time for human health effects. For human health, the approximately 20% that were not "on target" were overestimates, i.e., an overly conservative estimate of the chemical's toxicity. In fact, the SAR assessment for only one chemical was considered to have underestimated the chemical's toxicity. It should be noted that the data set required by the EU provides screening level information and does not address potential developmental, reproductive, neurotoxic, and carcinogenic effects. Nevertheless, based on this study and on the expertise of the OPPT SAR Team, OPP believes that SAR analysis is an effective tool for predicting toxicity and thus identifying chemicals which may present specific risk concerns and/or for which the value of generating additional data would be low.

Search for Existing Scientifically Valid Data

This was discussed in Unit IX. The Agency will review and evaluate this information.

Results of the Agency's Review and Evaluation of the Screening Data Set.

The screening level studies for Tier 2 chemicals (toxicity, environmental fate, ecotoxicity, and product chemistry) would be reviewed by the disciplinary specialists to determine if any adverse effects were present. Examples of adverse effects, for a toxicity study, could be organ lesions, malformations (missing limbs or cleft palette), or reduction in implant indices. OPP would not request that any additional studies (targeted testing) be submitted, if: (1) no adverse effects observed at the maximum tested dose (depending on the dose level), or no adverse effects observed in animals tested at a dose level of 1000 mg/kg/day, and (2) no concerns are raised from the SAR assessment or the evaluation of existing, scientifically valid data. If adverse effects are observed or if other concerns are identified, then under Tier 2 targeted testing would be requested. Targeted testing would address only the most sensitive observed adverse effects in the screening studies, and would typically call for submission of a guideline study(s) to address the effect of concern. However, it is also possible for OPP to determine based on the results of the screening level studies and/or the targeted testing that placement in Tier 3 would be appropriate.

Weight-of-the-Evidence Evaluation

As previously discussed, a chemical substance would be determined to be Tier 2 if a confirmatory judgement cannot be made concerning the chemical substance's low or low/moderate toxicity using commonly available information and/or an evaluation of existing, scientifically valid data. Therefore, for a Tier 2 chemical, at least the SAR assessment and the Tier 2 screening data set must be available for consideration during the weight-of-the-evidence evaluation. An SAR assessment is a powerful predictive tool that examines all toxicological disciplines. Thus, it may be possible for the SAR to support the findings from the screening-level combined repeated dose/developmental/reproductive toxicity study. Together with the evaluation of existing, scientifically valid data (if available) OPP would evaluate the potential for increased sensitivity for infants and children that is considered when making the safety finding under FFDCA. In a weight-of-the-evidence evaluation, all these sources of information/data are considered and then used to characterize the hazard associated with the use of an inert ingredient.

XVII. EVALUATION of the FQPA 10X SAFETY FACTOR WHEN CONDUCTING RISK ASSESSMENTS for LOWER TOXICITY CHEMICALS

A primary consideration in implementation of the FQPA safety factor provision is assessing the degree of concern regarding the potential for pre-and postnatal effects. On February 28, 2002, the Agency issued a Guidance Document entitled "Determination of the Appropriate FQPA Safety Factor(s) in Tolerance Assessment, which is available at http://www.epa.gov/pesticides/trac/science/#10-fold.

Because substances that may be considered to be Tier 1 pose much lower risks than conventional active ingredients, EPA considers a different evaluation process of the FQPA 10X safety factor to be appropriate for such substances. FFDCA section 408 provides that EPA shall apply an additional tenfold margin of safety for infants and children in the case of threshold effects to account for prenatal and postnatal toxicity and the completeness of the data base unless EPA concludes that a different margin safety will be safe for infants and children. Tier 1 chemicals will be those of low or low/moderate toxicity and the risk assessment usually will be qualitative. Because the criteria for a Tier 1 determination preclude evidence of significant toxicity, a safety factor analysis would not be used and the FQPA 10X safety factor will be unnecessary. If there were information associating significant reproductive or developmental effects with a chemical substance with a preliminary Tier 1 determination, then the chemical substance could undergo a quantitative risk assessment, or would be changed to Tier 2 or Tier 3.

For chemicals that may be considered to be Tier 2, the FQPA 10X safety factor cannot be removed or reduced without the submission of some type of developmental or reproductive data. For quantitative Tier 2 risk assessments, OPP would determine an actual number for the children's health safety factor. The determination would be based on the completeness of the screening toxicity database and the SAR assessment. For a Tier 2 chemical, the determination to remove, reduce, or retain the 10X would be made in a two-step process. The first step considers only the toxicity of the chemical. If, (1) the SAR assessment does not indicate the potential for reproductive and/or developmental effects or sensitivity, and (2) the available toxicity data, both the submitted study(ies) and an evaluation of existing, scientifically valid data, do not indicate any developmental/reproductive concerns or sensitivity, then the 10X may be removed based only on toxicity.

The second step in the process considers the exposure component of the risk assessment. As previously explained, a bounding estimate/LOC (level of concern) approach would be used to address dietary and residential exposures. After the bounding estimates are performed, the 10X will be reconsidered in light of the available information on exposure and the information from the bounding estimate/LOC (level of concern).

XVIII. ROLE of the INERT INGREDIENT FOCUS GROUP

To expedite the screening and review of low toxicity inert ingredients, OPP formed an Inert Ingredient Focus Group (IIFG). The IIFG has the primary decision-making role for the review and evaluation of Tier 1 and Tier 2 chemical substances. It is a senior level interdivisional group, whose members possess expertise in the various scientific and regulatory disciplines necessary for performing a risk assessment as well as making risk management decisions. Generally, the IIFG would not perform the initial science reviews or the preliminary risk assessments, but would evaluate those reviews and assessments as a group. Thus, the IIFG would simultaneously fulfill the roles of all the disciplinary and review committees that would ordinarily participate in assessing the risk of a conventional pesticide active ingredient, as well as being responsible for making the risk management determinations.

The types of decisions made by the IIFG would vary based upon the substance(s) being considered and the type of risk assessment being performed. At most IIFG meetings, the group would consider inert ingredients. However, some active ingredients, especially those that can also be used as inert ingredients, for which there is existing scientifically valid data that could be used to make the confirmatory judgement concerning the substances' low or low/moderate toxicity would also be considered for evaluation by the IIFG.

Some examples of the possible decisions that would be made by the IIFG are listed below:

- Determining the preliminary Tier determination as well as changes to this determination
- Determining the adequacy of the substances' database for performing a risk assessment
- Evaluating the extra factor for the protection of infants and children
- Determining for those substances' whose database are inadequate, the additional information/studies needed
- Judging the adequacy of the risk assessment performed for approving the use of the substance with or without limitations
- Identifying effects of concern and then determining the need for targeted testing
- Identifying the data needed prior to the issuance of a Data Call-In Notice
- Determining appropriate List placement (such as 4A) for an inert ingredient

The current process begins by selecting a chemical substance for review. The next steps, performed by various OPP staff, would be internet searches, data review and evaluation, and

document preparation. If necessary and appropriate, an SAR assessment would be prepared. IIFG would review the evaluations, and then determine the nature and extent of the risk assessment. OPP staff would then perform a preliminary risk assessment. The IIFG would then review and evaluate this risk assessment. For each Tier, the elements listed below comprise a possible sequence of events:

Tier 1a:

- Consider the available information and/or reviews and evaluate whether the preliminary determination as Tier 1a is appropriate
- Formulate a rationale indicating the substance's (or group of substances') low toxicity based on readily available information which can include factors such as a long history of safe use
- Determine whether the rationale is sufficient and appropriate considering a wide-ranging exposure pattern
- Determine whether the inert ingredient should be classified as List 4A or 4B
- Prepare a Decision Memo capturing the basis upon which the decision was made, which can then be used to prepare tolerance reassessment documents, Federal Register Notices, or other documents necessary to formalize the decision.

Tier 1b:

- Consider the available information and/or reviews and evaluate whether the preliminary determination as Tier 1b is appropriate
- Evaluate the results of searches for existing scientifically-valid data to determine the adequacy of the database
- If necessary and appropriate, have a SAR assessment prepared
- Formulate a rationale indicating the low or low/moderate toxicity based on the review of the existing scientifically valid data and/or the SAR assessment
- Consider a wide-ranging exposure pattern, and understand the non-pesticidal exposures of the chemical substance
- Determine whether a qualitative risk assessment or a quantitative risk assessment should be performed, or that the substance should be shifted to Tier 2
- Determine whether the inert ingredient should be classified as List 4A or 4B
- Prepare a Decision Memo capturing the basis upon which the decision was made, which can then be used to prepare tolerance reassessment documents, Federal Register Notices, or other documents necessary to formalize the decision.

Tier 2:

- Consider the available information and/or reviews and evaluate whether the preliminary determination as Tier 2 is appropriate
- Evaluate the results of searches for existing scientifically-valid data to determine the adequacy of the substances' database
- Understand the non-pesticidal exposures of the chemical substance
- If necessary and appropriate, have a SAR assessment prepared
- Determine whether the submitted data are sufficient and appropriate for making a decision, whether targeted testing is necessary, or whether there are significant risk concerns and that the substance should be shifted to Tier 3
- Consider and then integrate the existing scientifically valid data, the SAR assessment, and the reviews of the submitted data
- Select doses and endpoints for use in risk assessment
- Determine the appropriate safety factor for the protection of infants and children
- Perform the bounding level/LOC assessments
- Determine whether the inert ingredient should be classified as List 4A or 4B
- Prepare a Decision Memo capturing the basis upon which the decision was made, which can then be used to prepare tolerance reassessment documents, Federal Register Notices, or other documents necessary to formalize the decision.

Tier 3:

The IIFG would have little involvement with Tier 3 chemicals. The IIFG would make the Tier 3 determination. Once this determination has been made, the chemical would be referred to the appropriate regulatory manager in one of OPP's regulatory divisions.

Description of the Documentation

IIFG decision documents will contain: (1) the chemical name, and CAS Reg. No., (2) the requested action (e.g., tolerance exemption petition, tolerance reassessment), (3) the names of those present at the meeting (member, presenter, observer), (4) a discussion of the information/data reviewed and evaluated and/or a discussion of the risk of the chemical substance, and (5) recommendations from the IIFG to the management of the appropriate regulatory division.

Description of the Databases

Given the streamlined nature of this process, it is particularly important to capture chemical-specific information and decisions in searchable databases. This would allow the IIFG to compare new actions with previous decisions. OPP will establish an internal Agency searchable structure database containing the following information: (1) chemical name (common and CA Index Name), and CAS Reg. No., (2) structure, (3) petition number(s), (4) MRIDs, (5) exposure information such as types of formulations, (6) molecular formula, (7) human health toxicity - description of the data base and summary of review and evaluation, (8) ecotox summary, (9) fate summary, (10) water modeling estimates, (11) other information as well as the decision of the IIFG with rationale. There will also be an internal database to capture the complete IIFG decision document(s) as well as any other documents that were generated in support of the decision.

XIX. OPPORTUNITIES for REGISTRANTS and PETITIONERS

A person who has petitioned the Agency to grant an exemption from the requirement of a tolerance for an inert ingredient not currently used in pesticide products or a person who has submitted information to the Agency to support a particular tolerance exemption as part of tolerance reassessment may submit data on its own initiative, and may in certain cases be required to submit certain additional data. In all these instances, the Agency needs the submitted information to be properly formatted. The Agency needs sufficient credible information with which to make its decision, not an overwhelming amount of information.

As discussed the IIFG's first task is a preliminary tier determination. Proponents of a tolerance exemption are encouraged to propose a preliminary tier determination to OPP. Recommendations that are based on existing scientifically-valid information/data, and that clearly explain the factual basis for the recommended Tier determination, are those most likely to provide the information that could expedite the IIFG's Tier determination. The submitter should carefully consider the examples given in this document as well as evaluations performed by the IIFG in preparing their recommendation for preliminary Tier determination.

For substances believed to be Tier 1:

- For those chemical substances subject to tolerance reassessment, OPP expects that for many of these chemicals there would be sufficient, credible scientifically-valid information/data through the internet. Therefore, tolerance reassessments for many Tier 1 chemical substances would be performed by OPP without the need for submissions from those proponents of the tolerance reassessment.

- For a chemical substance for which a petitioner is seeking approval of a new inert ingredient (tolerance exemption petition), the petitioner should provide the Agency with the results of their search for existing scientifically valid information/data. The petitioner would then develop a rationale which explains why a tolerance exemption should be established for this low or low/moderate toxicity substance. The petitioner should also prepare a summary to be used in the Notice of Filing which would include the above information.

For substances believed to be Tier 2 and 3:

- For chemical substances subject to tolerance reassessment, proponents of a tolerance exemption should anticipate OPP's need for more information. Given that OPP's lack of credible scientifically-valid information/data can be the reason for a Tier 2 determination, if no information has been submitted to the Agency for a Tier 2 chemical substance, then the Agency would issue a FIFRA section 3(c)(2)(B) Data Call In (DCI)

Notice for the required information or request information under FFDCA 408(f) for the Tier 2 screening data set. For most Tier 3 chemicals, OPP will need the complete 40 CFR Part 158 data set.

- For a tolerance or tolerance exemption petition, the Agency will not be able to grant the petition unless there are sufficient data to determine that there is a reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue. The submission should include studies (formatted according to PR Notice 86-5), and the results of the search for existing scientifically valid information/data, and a summary to be used in the Notice of Filing, which will include discussions of the studies, the other uses of the chemical, and estimates of endpoints for use in risk assessment.

The Agency would conduct an initial evaluation of the submission including the submitters' recommendation for Tier determination. The submitter will be informed as to the completeness of the submission and whether any deficiencies have been identified.